

# PATENT SPECIFICATION

NO DRAWINGS

Inventors: DAVID GORDON PARSONS, ALAN FREDERICK TURNER and  
BRIAN GEORGE MURRAY

L133,406



**L133,406**

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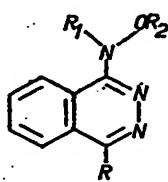
## COMPLETE SPECIFICATION

### Substituted 1-Amino Phthalazines

We, VANTOREX LIMITED, a British Company, of Loughborough, Leicestershire, do hereby declare the invention, for which we pray that a patent may be granted to us, and 5 the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to substituted phthalazines and more particularly to substituted 1-hydroxyl-amino phthalazines.

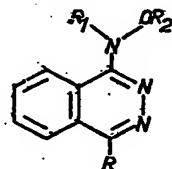
10 British Patent Specification No. 1,094,044 describes and claims a substituted 1-amino phthalazine of the formula:—



- 15 where R is hydrogen, a lower alkyl group, a lower alkoxy group, a di-lower alkyl amino-lower alkoxy group, a phenyl group, a phenyl-lower alkyl group, a pyridyl-lower alkyl group, a carbo-lower alkoxy-lower alkyl group, a carbo-lower alkyl group, a carbonyl-lower alkyl group, a carbonyl-lower alkyl group or an anilino group; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; 20 wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; and wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more lower alkyl, lower alkoxy, nitro, halo, amino, di-lower alkyl amino, or carboxy groups, which process comprises reacting a 1-halo-4-R-phthalazine of 25 and/or the phenyl group(s) of the R and/or

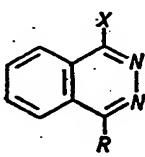
R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups.

30 British Patent Specification No. 1,094,044 also describes and claims a process for producing a substituted 1-amino phthalazine of the formula:—



40 wherein R is hydrogen, a lower alkyl group, a lower alkoxy group, a di-lower-alkylamino-lower alkoxy group, a phenyl group, a phenyl-lower alkyl group, a pyridyl-lower alkyl group, a carbo-lower alkoxy-lower alkyl group, a carbamyl-lower alkyl group, or an anilino group; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group, or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen or a lower alkyl group; and wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more lower alkyl, lower alkoxy, nitro, halo, amino, di-lower alkyl amino, or carboxy groups, which process comprises reacting a 1-halo-4-R-phthalazine of 45 and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more lower alkyl, lower alkoxy, nitro, halo, amino, di-lower alkyl amino, or carboxy groups, which process comprises reacting a 1-halo-4-R-phthalazine of 50 and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more lower alkyl, lower alkoxy, nitro, halo, amino, di-lower alkyl amino, or carboxy groups, which process comprises reacting a 1-halo-4-R-phthalazine of 55 and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more lower alkyl, lower alkoxy, nitro, halo, amino, di-lower alkyl amino, or carboxy groups, which process comprises reacting a 1-halo-4-R-phthalazine of

[Prior]



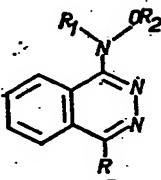
wherein X is a halogen, with a substituted hydroxy-amine of the formula:—



- 5 in the presence of an anhydrous sodium acetate and an inert, non-reactive organic solvent, so as to produce the desired substituted 1-amino phthalazine.

The present invention relates to modifications of the compounds claimed in the parent specification and to the preparation of such modified compounds.

Accordingly the present invention provides a substituted 1-aminophthalazine of the formula:—



wherein R is a lower alkoxy-lower alkyl group, a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, a di-lower alkyl amino-lower alkyl group, a cyclic saturated organic base-lower alkyl group, a cyclic saturated organic base-lower alkoxy group, a cyclic saturated organic base group, or a di-lower alkyl amino group; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base when present may be substituted with one or more lower alkyl groups.

As used throughout the present specification, the terms "lower alkyl" and "lower alkoxy" embrace both straight and branched chain alkyl and alkoxy radicals, respectively, containing from 1 to 6 carbon atoms. For example, the term "lower alkyl" includes methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl and 2,3-dimethylbutyl and the term "lower alkoxy" includes methoxy, ethoxy, n-propoxy, iso-

propoxy, n-butoxy, tert-butoxy, n-amyloxy, sec-amyloxy, n-hexyloxy, 2-ethylbutyloxy and 2,3-dimethylbutyloxy. "Halogen" is meant to include bromine, chlorine, fluorine and iodine.

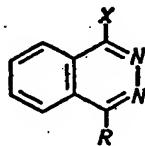
The term "cyclic saturated organic base" embraces all simply saturated nitrogenous bases. In addition to the basic nitrogen atom the saturated ring system may include for example a hetero-oxygen or nitrogen atom. The cyclic saturated organic bases may have one or more lower alkyl substituents attached thereto. Examples of suitable cyclic saturated organic base groups include pyrrolidino, piperidino, piperazino morpholino, and N-methyl piperazino groups. An example of a compound in accordance with the present invention wherein the substituent R is a cyclic saturated organic base group is 1-hydroxylamino-4-piperidino phthalazine.

The compounds of the present invention are solid crystalline materials. Infra-red spectral data and elemental analysis, taken together with the nature of the starting materials and mode of synthesis, confirms their structure.

Further the compounds of the present invention have significant pharmacological activity, without demonstrable adverse toxicity, as antipyretic, anti-inflammatory, hypotensive, bronchodilator, and respiratory stimulant agents as determined by recognised and accepted pharmacological test procedures.

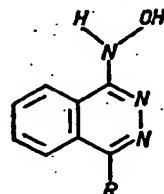
In addition, as in the case of the compounds described and claimed in British Patent Specification No. 1,094,044, the compounds of the present invention are valuable as chemical intermediates in the synthesis of other substituted phthalazines having significant pharmacological activity. The mode of preparation of these further derivatives is described and claimed in British Patent Specifications Nos. 1,094,045 and 1,094,046.

The following reaction sequence illustrates one method of preparation of the compounds of the present invention:—



STARTING MATERIAL

↓ HYDROXYLAMINE



FINAL PRODUCT

wherein X is halogen and R is as hereinabove described, a lower alkoxy-lower alkyl group (such as a methoxymethyl group), a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, a di-lower alkyl amino-lower alkyl group, a cyclic saturated organic base-lower alkyl group, a cyclic saturated organic base-lower alkoxy group, a cyclic saturated organic base group, or a di-lower alkyl amino group. The starting materials for the preparation of the compounds of the present invention by the foregoing reaction sequence are readily prepared by the method described by A. Leick, Ber. 38: 2918 (1905) and J. Druy et al. Helv. Chim. Acta, 34: 195-210 (1951).

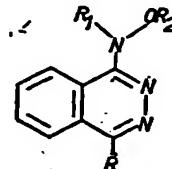
According to the reaction sequence depicted above, the starting material is converted to the compounds of the present invention by refluxing a 1-halophthalazine starting material, or one of its appropriately 4-substituted-1-halophthalazine equivalents as above defined, with hydroxylamine in the presence of anhydrous sodium acetate and an inert, non-reactive organic solvent, such as for example, methanol, ethanol.

Starting materials wherein the benzene ring of the phthalazine nucleus and/or the benzene ring of a phenoxy, R substituent bears one or more halogen atoms or lower alkyl, nitro, amino, di-lower alkylamino, carboxy or lower alkoxy groups, or wherein the cyclic saturated organic base group, R, when present bears one or more lower alkyl substituents, are prepared by the same procedures set forth in the Leick and Druy papers referred to hereinabove, and are the full equivalents of the above specific starting materials. Their use in the above described reaction sequence results in the preparation of products having lower alkyl, nitro, halogen, amino, di-lower alkylamino, carboxy or lower alkoxy substituents at the same place as in the starting materials, such products having the same utility as the specific products depicted in the above reaction sequence.

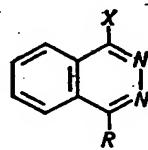
As equivalent reactants in the foregoing reaction sequence to hydroxylamine, there may be employed substituted hydroxylamines of the formula  $R_1HN-OR_2$ , wherein  $R_1$  is hydrogen, lower alkyl, phenyl, phenyl-lower alkyl, or phenyl-lower alkyl wherein the phenyl group bears one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl-amino, or carboxy groups and  $R_2$  is hydrogen or lower alkyl, at least one of  $R_1$  and  $R_2$  being other than hydrogen. The use of such substituted hydroxylamines in the reaction sequence results in the preparation of compounds of this invention wherein the nitrogen atom of the hydroxylamino substituent at the 1-position

of the nucleus bears  $R_1$  and  $OR_2$  substituents corresponding to the reactant used, such products having the same utility as the specific products described above and being included within the scope of the invention.

According to the above the present invention provides a process for producing a substituted 1-amino-phthalazine of the formula:—



wherein R is a lower alkoxy-lower alkyl group, a phenoxy group, a hydroxy-lower alkoxy group, a di-lower alkylamino-lower alkyl group; a cyclic saturated organic base-lower alkyl group, a cyclic saturated organic base-lower alkoxy group, a cyclic saturated organic base group, or a di-lower alkyl amino group; wherein  $R_1$  is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein  $R_2$  is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or  $R_1$  substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base when present may be substituted with one or more lower alkyl groups which process comprises reacting a 1-halo-4-R-phthalazine of the formula:—



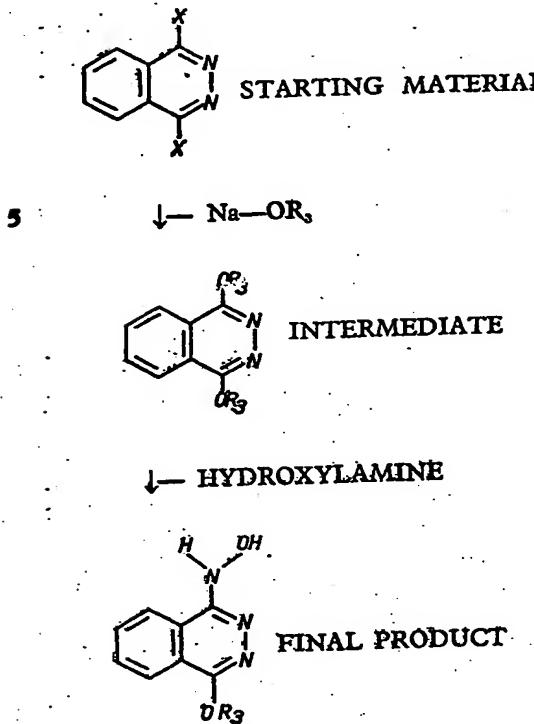
wherein X is a halogen, with a substituted hydroxylamine of the formula:—



in the presence of anhydrous sodium acetate and an inert, non-reactive organic solvent, so as to produce the desired substituted 1-amino phthalazine.

Where the substituent in the 4-position contains an oxygen atom through which it is

linked to the phthalazine nucleus an alternate synthesis is preferred. This may be represented by the following reaction sequence:



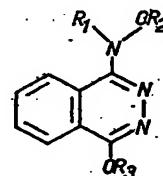
- 10 wherein X is halogen and the group —OR<sub>3</sub> is a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, or a cyclic saturated organic base-lower alkoxy group, said group being linked to the phthalazine nucleus via the oxygen atom O.
- 15 The starting material for preparing the compounds of this invention, using the above-described alternate synthetic sequence, is a 1,4-dihalophthalazine, for example, 1,4-dichlorophthalazine. Such starting materials are commercially available or may be prepared as described by Hirsch and Orphanos, Can. J. Chem. 43: 2708-10 (1965), who treat 1,4-phthalazinedione with a phosphorous pentahalide, for example phosphorus pentachloride, at atmospheric pressure in the presence of a halogenated solvent.

In carrying out the above-described reaction sequence, the starting material is first converted to a 1,4-di-lower alkoxy- or 1,4-diphenoxypyphthalazine by treatment with an appropriate sodium alcoholate or sodium phenolate. Such 1,4-di-lower alkoxy- and 1,4-diphenoxypyphthalazines are described, to-

gether with the method of their preparation by Elvidge and Redman, J. Chem. Soc. 1710 (1965). The 1,4-di-lower alkoxy- or 1,4-diphenoxypyphthalazine intermediate is then treated with hydroxylamine or an equivalent thereof, for example, methoxyamine, in an inert solvent such as methanol and in the presence of anhydrous sodium acetate. The reaction products may be recovered by conventional techniques of isolation and crystallization.

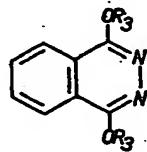
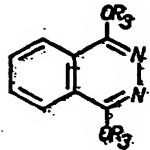
As with the previous preparative procedure hereinabove described, any of the substituted hydroxylamines mentioned may be employed in place of the hydroxylamine. Starting materials wherein the benzene ring of the phthalazine nucleus and/or the benzene ring of the sodium phenolate, when employed, bears one or more lower alkyl, nitro, halogen, amino, di-lower alkyl amino, carboxy or lower alkoxy substituents, when used in the above reaction procedure result in the preparation of correspondingly substituted products. Such products have the same utility as the specific products depicted in the above reaction sequence.

According to the foregoing the present invention further provides a process for producing a substituted 1-amino phthalazine of the formula:—



wherein the group —OR<sub>3</sub> is a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, or a cyclic saturated organic base-lower alkoxy group said group being linked to the phthalazine nucleus via the oxygen atom, O; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group when present may be substituted with one or more lower alkyl groups, which process comprises reacting a compound of the formula:—

so as to produce an intermediate compound of the formula:—

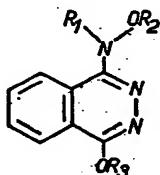


with a substituted hydroxylamine of the formula:—



- 5 in the presence of an inert, non-reactive solvent and anhydrous sodium acetate, so as to produce the desired substituted 1-amino-phthalazine.

- 10 The invention also provides a process for producing a substituted 1-amino phthalazine of the formula:—



- 15 wherein the group —OR<sub>3</sub> is a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, or a cyclic saturated organic base-lower alkoxy group, said group being linked to the phthalazine nucleus by the oxygen atom, O; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group when present may be substituted with one or more lower alkyl groups, which process comprises reacting a 1,4-dihalo phthalazine with a sodium alcoholate or sodium phenolate of the formula:—

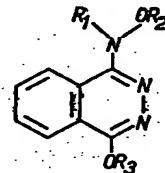


and subsequently reacting said intermediate compound with a substituted hydroxylamine of the formula:—



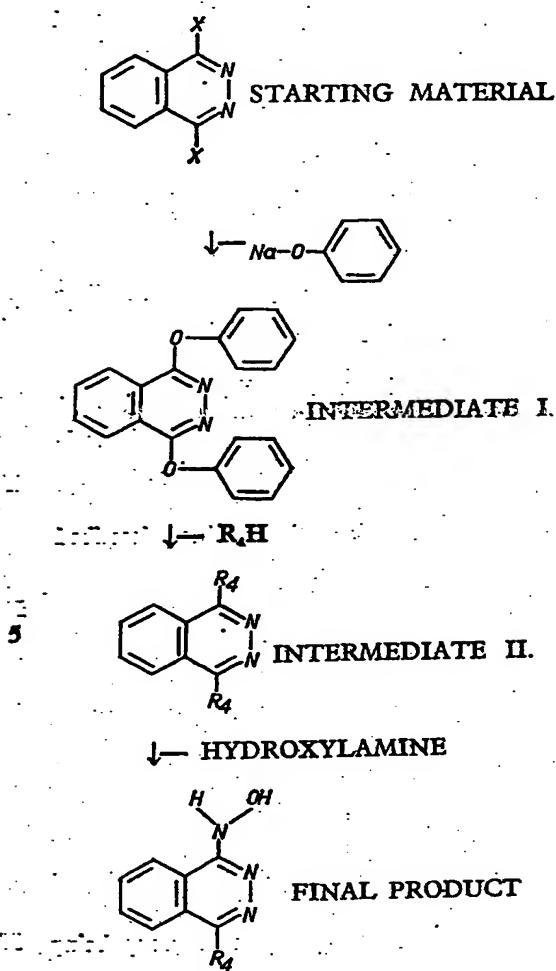
in the presence of an inert, non-reactive solvent and anhydrous sodium acetate, so as to produce the desired substituted 1-amino-phthalazine.

In a modification of the above-described process the present invention provides a process for preparing a substituted 1-amino phthalazine of the formula:—



wherein R<sub>1</sub> and R<sub>2</sub> are as hereinbefore described and wherein the group —OR<sub>3</sub> is a lower alkoxy group or a di-lower alkyl amino-lower alkoxy group, said group being linked to the phthalazine nucleus through the oxygen atom, O. The process is exactly as that set forth above for the preparation of derivatives wherein the substituent at the 4-position is attached to the phthalazine nucleus through its oxygen atom, except in that when preparing the intermediate the appropriate alternative sodium alcoholate is employed.

In the case of compounds according to the present invention wherein the substituent at the 4-position is a cyclic saturated organic base group, or a di-lower alkyl amino group it is preferred to employ a reaction sequence, which may be represented as follows:—

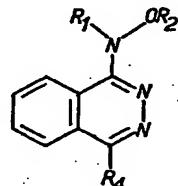


wherein X is halogen and R<sub>4</sub> is a cyclic saturated organic base group linked to the phthalazine nucleus by the nitrogen atom, or a lower alkyl derivative thereof such as pyrrolidino, piperidino, piperazino, morpholino, or N-methyl-piperazino, or a di-lower alkyl amino group.

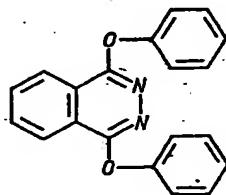
In carrying out this reaction sequence the starting material is the same as that employed in the previously described preferred reaction sequence leading to oxygen-linked substitution at the 4-position of the phthalazine nucleus. Preparation of the 1,4-diphenoxypyphthalazine intermediate, I, is also as described above. Conversion of the 1,4-diphenoxypyphthalazine intermediate to the phthalazine intermediate, II, is carried out by treatment with the appropriate di-lower alkyl amine or cyclic saturated organic base at reflux temperature with the base also serving as solvent for the reaction. This method is also described in the Elvidge and Redman reference, where preparation of the specific 1,4-di-N-morpholinophthalazine is described.

Conversion of this intermediate is then obtained by treatment with hydroxylamine, or an equivalent thereof as hereinabove described, such as, for example, methoxyamine, in an inert solvent such as methanol and in the presence of anhydrous sodium acetate. The reaction products are recovered by conventional techniques of isolation and crystallization. Once again the phthalazine nucleus of the starting material may be substituted as described previously to give a correspondingly substituted end product.

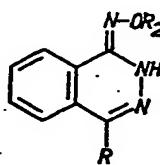
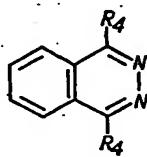
In accordance with the foregoing the present invention provides a process for producing a substituted 1-amino phthalazine of the formula:—



wherein the group R<sub>4</sub> is a cyclic saturated organic base group linked to the phthalazine nucleus by the nitrogen atom, or a di-lower alkylamino group wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group of the R<sub>1</sub> substituent when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group may be substituted with one or more lower alkyl groups, which process comprises reacting a 1,4-dihalo-phthalazine with sodium phenolate so as to produce a 1,4-diphenoxypyphthalazine of the formula:—



subsequently reacting said 1,4-diphenoxypyphthalazine with a di-lower alkylamine or cyclic saturated organic base at reflux temperature so as to produce an intermediate compound of the formula:—



and finally reacting said intermediate compound with a substituted hydroxylamine of the formula:—



in the presence of an inert non-reactive solvent and in the presence of anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

10 Preparation of the substituted 1-amino phthalazine from the second intermediate and the 1,4-diphenoxyl phthalazine is also contemplated.

15 In carrying out the above-described reaction sequence, the starting material is first converted to a 1,4-di-lower-alkoxy- or 1,4-diphenoxylphthalazine by treatment with an appropriate sodium alcoholate or sodium phenolate. Such 1,4-di-lower alkoxy and 1,4-diphenoxylphthalazines are described, together with the method of their preparation by Elvidge and Redman, J. Chem. Soc. 1710 (1965). The 1,4-di-lower alkoxy- or 1,4-diphenoxylphthalazine intermediate is then treated with hydroxylamine or an equivalent thereof, for example, methoxyamine, in an inert solvent such as methanol and in the presence of anhydrous sodium acetate. The reaction products may be recovered by conventional techniques of isolation and crystallisation.

20 The compounds of the invention wherein the substituent at the 1-position is a radical of the formula  $R_1NOH$ ,  $R_1$  being as described above, are readily converted into esters by treatment with a lower alkyl carboxylic anhydride such as acetic anhydride, thereby converting the OH group into a radical of the formula  $-O-CO-$  lower alkyl. Such esters are the full equivalents of the non-esterified hydroxylamino compounds from which they are derived and are included within the scope of the invention.

25 The compounds of the present invention wherein the substituent at the 1-position is a radical of the formula  $HN-OR_2$  wherein  $R_2$  is hydrogen or lower alkyl are capable of existing in the tautomeric hydroxylimino form:

30 The compounds of the present invention wherein the substituent at the 1-position is a radical of the formula  $HN-OR_2$  wherein  $R_2$  is hydrogen or lower alkyl are capable of existing in the tautomeric hydroxylimino form:

35 Such tautomers are wholly equivalent to the 1-hydroxylamino substituted compounds described above and are included within the scope of the present invention.

The compounds of the present invention can, if desired, be converted into their non-toxic pharmaceutically acceptable acid-addition and quaternary ammonium salts. Acid addition salts which may be formed comprise, for example, salts with inorganic acids, such as the hydrochloride, hydrobromide, hydroiodide, sulphate, and phosphate. They may also comprise salts with organic acids, including monobasic acids such as the acetate or the propionate, and especially those with hydroxy organic acids and dibasic acids, such as the citrate, tartrate, malate and maleate. Pharmaceutically, the salt will not be substantially more toxic than the compound itself and, to be acceptable, it should be able to be incorporated into conventional liquid or solid pharmaceutical media. Among the useful quaternary ammonium salts are those formed by such alkyl halides as methyl iodide and n-hexylbromide. Such pharmaceutically useful acid-addition and quaternary ammonium salts are the full equivalents of the bases from which they are derived and are included within the scope of the present invention.

40 The compounds of the invention, either as free bases or in the form of a non-toxic pharmaceutically acceptable acid-addition or quaternary ammonium salt, can be combined with pharmaceutical diluents and carriers to form such dosage forms as tablets, suspensions, solutions, and suppositories.

45 Also the present invention provides a method for treating vertebrates other than man which comprises administering a compound as claimed herein, or a non-toxic pharmaceutically acceptable acid addition or quaternary ammonium salt thereof.

The following Examples illustrate the processes of the present invention.

#### EXAMPLE 1

##### 1-Hydroxylamino-4-ethoxyphthalazine:

(a) 1,4-Diethoxyphthalazine: 1,4-Dichlorophthalazine (1100 g.) is added portionwise over a 30 minute period to a cooled solution of sodium ethoxide

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(4.5 liters). The reaction mixture is then refluxed for 1 hour followed by treatment with Dicalite and filtration. The product crystallizes upon cooling and is collected and washed.

(b) 1 - Hydroxylamino - 4 - ethoxyphthalazine: A mixture of the 1,4-diethoxyphthalazine (1000 g.), prepared as described in step (a), anhydrous sodium acetate (1880 g.) and hydroxylamine hydrochloride (956 g.) in methanol (7.0 liters) are refluxed with stirring for 6 hours. The reaction mixture was cooled and the product filtered off, washed and dried to yield 911.7 g. (97%) yellow needles, m.p. 201°—204°C. (d)

Analysis:  
Calculated for  $C_{10}H_{11}N_3O_2$ :  
C, 58.5; H, 5.4; N, 20.5  
Found:  
C, 58.5; H, 5.4; N, 20.5

In like manner the following were also prepared:

Calculated for  $C_{12}H_{16}N_4O_2 \cdot HCl \cdot H_2O$ :  
C, 47.60; H, 6.33; Cl, 11.71; N, 18.51  
Found:  
C, 47.73; H, 6.14; Cl, 11.81; N, 18.30

**EXAMPLE 5**  
1 - Methoxyamino - 4 - dimethylaminoethoxyphthalazine from 1,4-bis-(2-dimethylaminoethoxy)phthalazine:  
m.p. 93°—94°C.  
Analysis:  
Calculated for  $C_{13}H_{18}N_4O_2$ :  
C, 59.52; H, 6.92; N, 21.36  
Found:  
C, 59.61; H, 7.13; N, 21.48

**EXAMPLE 6**  
1 - Hydroxylamino - 4 - diethylaminoethoxyphthalazine from 1,4-bis-(diethylaminoethoxy)phthalazine:  
m.p. 90°—91°C.  
Analysis:  
Calculated for  $C_{14}H_{20}N_4O_2$ :  
C, 60.85; H, 7.30; N, 20.28  
Found:  
C, 61.25; H, 7.04; N, 19.95

**EXAMPLE 7**  
1 - Hydroxylamino - 4 - (2 - N - piperidinoethoxy)phthalazine from 1,4 - di - (2 - N - piperidinoethoxy)phthalazine:  
m.p. 119°C.  
Analysis:  
Calculated for  $C_{15}H_{20}N_4O_2$ :  
C, 62.48; H, 6.99; N, 19.43  
Found:  
C, 62.36; H, 7.04; N, 19.15

**EXAMPLE 2**  
1 - Hydroxylamino - 4 - methoxyphthalazine from 1,4-dimethoxyphthalazine:  
m.p. (hydrochloride) 128°—130°C. 25

**EXAMPLE 3**  
1 - Methoxyamino - 4 - ethoxyphthalazine from 1,4-diethoxyphthalazine:  
m.p. 70°—72°C. 30  
Analysis:  
Calculated for  $C_{11}H_{13}N_3O_2$ :  
C, 60.26; H, 5.98; N, 19.16  
Found:  
C, 60.33; H, 5.95; N, 18.99 35

**EXAMPLE 4**  
1 - Hydroxylamino - 4 - dimethylaminoethoxyphthalazine from 1,4-bis-(2-dimethylaminoethoxy)phthalazine:  
m.p. 230°—233°C. 40  
Analysis (as monohydrochloride monohydrate):

**EXAMPLE 8**  
1 - Hydroxylamino - 4 - (2 - N - morpholinoethoxy)phthalazine from 1,4 - di - (2 - N - morpholinoethoxy)phthalazine:  
m.p. 151°C.  
Analysis:  
Calculated for  $C_{14}H_{18}O_3N_4$ :  
C, 57.92; H, 6.25; N, 19.30  
Found:  
C, 57.97; H, 6.37; N, 19.10 85

**EXAMPLE 9**  
1 - Hydroxylamino - 4 - (2 - hydroxyethoxy)phthalazine from di - 1,4 - (2 - hydroxyethoxy)phthalazine:  
m.p. 212°—222°C.  
Analysis:  
Calculated for  $C_{10}H_{11}N_3O_3$ :  
C, 54.3; H, 5.0; N, 19.0  
Found:  
C, 54.2; H, 5.1; N, 18.8 95

**EXAMPLE 10**  
1 - Methoxyamino - 4 - (2 - hydroxyethoxy)phthalazine from 1,4 - di - (2 - hydroxyethoxy)phthalazine;  
m.p. 99°—101°C.  
Analysis:  
Calculated for  $C_{11}H_{13}N_3O_3$ :  
C, 56.2; H, 5.6; N, 17.9  
Found:  
C, 56.1; H, 5.7; N, 18.0 100

**EXAMPLE 11**

1 - Hydroxylamino - 4 - (2 - methoxyethoxy)phthalazine from 1,4 - di - (2-methoxyethoxy)phthalazine:

5 m.p. 182°—185°C.

Analysis:

Calculated for  $C_{11}H_{13}N_3O_3$ :  
C, 56.2; H, 5.6; N, 17.9

10 Found:  
C, 56.2; H, 5.8; N, 17.9

**EXAMPLE 12**

1 - Hydroxylamino - 4 - phenoxyphthalazine from 1,4 - diphenoxypyphthalazine:  
m.p. 196°—200°C.

15 Analysis:

Calculated for  $C_{14}H_{11}N_3O_2$ :  
C, 66.4; H, 4.4; N, 16.6

Found:  
C, 66.6; H, 4.3; N, 16.7

**EXAMPLE 13**

1 - Hydroxylamino - 4 - N - morpholino-phthalazine:

(a) 1,4-Diphenoxypyphthalazine: Sodium phenoxide (58.3 g.), prepared by the addition of phenol to a solution of sodium in alcohol and evaporating to dryness, is reacted with 1,4-dichlorophthalazine (50 g.) in toluene (1000 ml.) by heating under reflux overnight. After evaporation of the solvent, the solid obtained is washed with hot water and then crystallized from ethyl acetate, giving colourless needles, (34.5 g., 49%), m.p. 220°—222°C.

(b) 1,4-Dimorpholinophthalazine: A solution of 1,4-diphenoxypyphthalazine (25 g.), prepared as described in step (a), in morpholine is heated under reflux overnight. The excess morpholine is then evaporated under reduced pressure and the residue washed with hot water. This is then recrystallized from dimethylformamide to give 12.1 g. of small needles, m.p. 205°—207°C.

(c) 1 - Hydroxylamino - 4 - morpholino-phthalazine: A solution of 1,4-dimorpholinophthalazine (20 g.) in methanol (150 ml.) was treated with hydroxylamine hydrochloride (13.9 g.) and sodium acetate (27.3 g.) and heated under reflux overnight. After cooling, the methanol is distilled away under vacuum and the residue shaken with warm water (250 ml.). After filtering, and washing with water and methanol, the crude product (14.8 g. 90.2%) is recrystallized from aqueous dimethylformamide to give pale yellow needles (12.1 g.) m.p. 210°—230°C. (d).

Analysis:

Calculated for  $C_{12}H_{14}N_4O_2$ :  
C, 58.5; H, 5.7; N, 22.75

Found:

C, 58.6; H, 5.6; N, 22.6

60 In like manner the following were also prepared:

**EXAMPLE 14**

1 - Hydroxylamino - 4 - N - (N - methylpiperazino)phthalazine from 1,4 - di - N - (N - methylpiperazino)phthalazine:  
m.p. 215°—217°C.

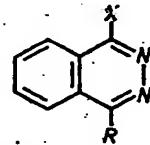
Analysis:

Calculated for  $C_{12}H_{14}N_4O$ :  
C, 60.2; H, 6.6; N, 27.0

Found:

C, 60.4; H, 6.8; N, 26.7

The following examples illustrate compounds prepared in accordance with the method hereinbefore described which comprises reacting hydroxylamine with a compound of the formula:—



where R and X are as hereinbefore defined.

**EXAMPLE 15**

1 - Hydroxylamino - 4 - (2 - diethylaminoethyl)phthalazine:  
m.p. 162°—163°C.

Analysis:

Calculated for  $C_{14}H_{20}N_4O$ :  
C, 64.6; H, 7.7; N, 21.5

Found:

C, 64.6; H, 7.8; N, 21.6

**EXAMPLE 16**

1 - Hydroxylamino - 4 - (2 - dimethylaminoethyl)phthalazine:  
m.p. 161°—162°C.

Analysis:

Calculated for  $C_{14}H_{18}N_4O$ :  
C, 62.1; H, 6.9; N, 24.1

Found:

C, 62.1; H, 6.9; N, 24.0

**EXAMPLE 17**

1 - Hydroxylamino - 4 - (2 - N - morpholinoethyl)phthalazine monohydrochloride:  
monohydrate:  
m.p. 260°—261°C.

Analysis:

Calculated for  $C_{14}H_{18}N_4O_2 \cdot HCl \cdot H_2O$   
C, 51.2; N, 6.4; Cl, 10.8; N, 17.0

Found:

C, 51.8; H, 6.4; Cl, 10.8; N, 16.6

**EXAMPLE 18**

1 - Hydroxylamino - 4 - (2 - N - piperidinoethyl)phthalazine monohydrochloride:  
m.p. 260°—263°C.

Analysis:

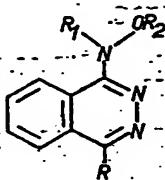
Calculated for  $C_{15}H_{22}N_4 \cdot HCl$   
C, 58.3; H, 6.9; Cl, 11.5; N, 18.1

Found:

C, 58.1; H, 6.9; Cl, 11.4; N, 17.9

## WHAT WE CLAIM IS:—

1. A substituted 1-amino phthalazine of the formula:—



5 wherein R is a lower alkoxy-lower alkyl group, a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, a di-lower alkyl amino-lower alkyl group, a cyclic saturated organic base-lower alkyl group, a cyclic saturated organic base-lower alkoxy group, a cyclic saturated organic base group, or a di-lower alkyl amino group; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base when present may be substituted with one or more lower alkyl groups.

10 2. A substituted 1-amino phthalazine as claimed in claim 1 wherein R is a cyclic saturated organic base group being a pyrrolidino, piperidino, piperazino, or morpholino group or a lower alkyl derivative thereof.

15 3. A substituted amino phthalazine as claimed in claim 1 wherein R is a cyclic saturated organic base-lower alkyl or a cyclic saturated organic base-lower alkoxy group; wherein the cyclic saturated organic base moiety is pyrrolidino, piperidino, piperazino, or morpholino or a lower alkyl derivative thereof.

20 4. 1 - Hydroxylamino - 4 - methoxy-methylphthalazine.

25 5. 1 - Hydroxylamino - 4 - (2 - diethylaminoethyl)phthalazine.

30 6. 1 - Hydroxylamino - 4 - (2 - dimethylaminoethyl)phthalazine.

35 7. 1 - Hydroxylamino - 4 - (2 - N-morpholinoethyl)phthalazine.

40 8. 1 - Hydroxylamino - 4 - (2 - N-piperidinoethyl)phthalazine.

45 9. 1 - Hydroxylamino - 4 - (2 - N-piperidinoethoxy)phthalazine.

50 10. 1 - Hydroxylamino - 4 - (2 - N-morpholinoethoxy)phthalazine.

55 11. 1 - Hydroxylamino - 4 - (2 - hydroxyethoxy)phthalazine.

60 12. 1 - Methoxylamino - 4 - (2 - hydroxyethoxy)phthalazine.

13. 1 - Hydroxylamino - 4 - (2 - methoxyethoxy)phthalazine.

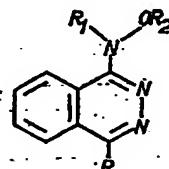
14. 1 - Hydroxylamino - 4 - phenoxyphthalazine.

15. 1 - Hydroxylamino - 4 - N - morpholino phthalazine.

16. 1 - Hydroxylamino - 4 - piperidino phthalazine.

17. 1 - Hydroxylamino - 4 - N(N-methyl piperazino)phthalazine.

18. A process for producing a substituted 1-aminophthalazine of the formula:—



70 wherein R is a lower alkoxy-lower alkyl group, a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, a di-lower alkyl amino-lower alkyl group; a cyclic saturated organic base-lower alkyl group, a cyclic saturated organic base-lower alkoxy group, a cyclic saturated organic base group, or a di-lower alkyl amino group; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base when present may be substituted with one or more lower alkyl groups.

75 2. A substituted 1-amino phthalazine as claimed in claim 1 wherein R is a cyclic saturated organic base group being a pyrrolidino, piperidino, piperazino, or morpholino group or a lower alkyl derivative thereof.

80 3. A substituted amino phthalazine as claimed in claim 1 wherein R is a cyclic saturated organic base-lower alkyl or a cyclic saturated organic base-lower alkoxy group; wherein the cyclic saturated organic base moiety is pyrrolidino, piperidino, piperazino, or morpholino or a lower alkyl derivative thereof.

85 4. 1 - Hydroxylamino - 4 - methoxy-methylphthalazine.

90 5. 1 - Hydroxylamino - 4 - (2 - diethylaminoethyl)phthalazine.

6. 1 - Hydroxylamino - 4 - (2 - dimethylaminoethyl)phthalazine.

7. 1 - Hydroxylamino - 4 - (2 - N-morpholinoethyl)phthalazine.

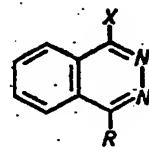
8. 1 - Hydroxylamino - 4 - (2 - N-piperidinoethyl)phthalazine.

9. 1 - Hydroxylamino - 4 - (2 - N-piperidinoethoxy)phthalazine.

10. 1 - Hydroxylamino - 4 - (2 - N-morpholinoethoxy)phthalazine.

11. 1 - Hydroxylamino - 4 - (2 - hydroxyethoxy)phthalazine.

12. 1 - Methoxylamino - 4 - (2 - hydroxyethoxy)phthalazine.



95 wherein X is a halogen, with a substituted hydroxylamine of the formula:—

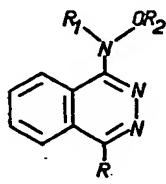


in the presence of anhydrous sodium acetate and an inert, non-reactive organic solvent, so as to produce the desired substituted 1-amino phthalazine.

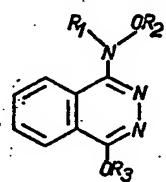
100 19. A process for preparing a substituted 1-amino phthalazine of the formula:—

groups, which process comprises reacting a compound of the formula:—

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- wherein R is a lower alkoxy-lower alkyl group, a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, a di-lower alkylamino-lower alkyl group, a cyclic saturated organic base-lower alkyl group, a cyclic saturated organic base-lower alkoxy group, or a cyclic saturated organic base group; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group, or a phenyl-lower alkyl group; wherein R<sub>2</sub> is an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups, and wherein the cyclic saturated organic base when present may be substituted with one or more lower alkyl groups, which process comprises treating a suitably substituted 1-aminophthalazine wherein R<sub>2</sub> is hydrogen with a lower alkyl carboxylic anhydride, so as to produce the desired substituted 1-amino phthalazine.
20. A process for producing a substituted 1-amino phthalazine of the formula:—



- 30 wherein the group —OR<sub>3</sub> is a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, or a cyclic saturated organic base-lower alkoxy group said group being linked to the phthalazine nucleus by the oxygen atom, O; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group, or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group when present may be substituted with one or more lower alkyl groups, which process comprises reacting a 1,4 dihalo phthalazine with a sodium alcoholate or sodium phenolate of the formula:—
- 35

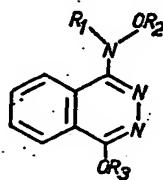


in the presence of an inert, non-reactive solvent and anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

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21. A process for producing a substituted 1-amino phthalazine of the formula:—

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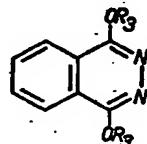
wherein the group —OR<sub>3</sub> is a phenoxy group, a hydroxy-lower alkoxy group, a lower alkoxy-lower alkoxy group, or a cyclic saturated organic base-lower alkoxy group said group being linked to the phthalazine nucleus by the oxygen atom, O; wherein R<sub>1</sub> is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein R<sub>2</sub> is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or R<sub>1</sub> substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group when present may be substituted with one or more lower alkyl groups, which process comprises reacting a 1,4 dihalo phthalazine with a sodium alcoholate or sodium phenolate of the formula:—

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so as to produce an intermediate compound of the formula:—

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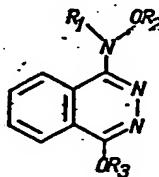
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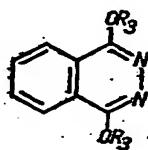
and subsequently reacting said intermediate compound with a substituted hydroxylamine of the formula:—



- 5 in the presence of an inert, non-reactive solvent and anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.
- 10 22. A modification of the process claimed in claim 20 for producing a substituted 1-amino phthalazine having the formula:—



- 15 wherein the group  $-OR_3$  is a lower alkoxy group or a di-lower alkyl amino-lower alkoxy group linked to the phthalazine nucleus by the oxygen atom, O; wherein  $R_1$  is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein  $R_2$  is hydrogen, a lower alkyl group or an alkanoyl group; and wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or  $R_1$  substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkylamino, or carboxy groups which process comprises reacting a compound of the formula:—
- 20
- 25

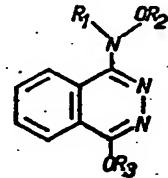


- 30 with a substituted hydroxylamine of the formula:—



- in the presence of an inert, non-reactive solvent and anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

23. A modification of the process claimed in claim 21 for producing a substituted 1-amino phthalazine having the formula:—



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wherein the group  $-OR_3$  is a lower alkoxy group, or a di-lower alkyl amino-lower alkoxy group linked to the phthalazine nucleus by the oxygen atom, O, wherein  $R_1$  is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein  $R_2$  is hydrogen, a lower alkyl group or an alkanoyl group; and wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group(s) of the R and/or  $R_1$  substituents when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkylamino, or carboxy groups which process comprises reacting a 1,4 dihalo phthalazine with a sodium alcoholate or sodium phenolate of the formula:—

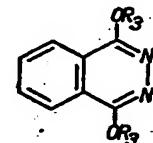
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so as to produce an intermediate compound of the formula:—



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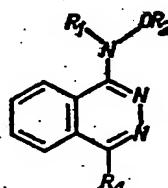
and subsequently reacting said intermediate compound with a substituted hydroxylamine of the formula:—



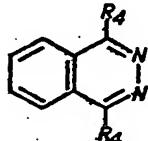
in the presence of an inert, non-reactive solvent and anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

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24. A process for producing a substituted 1-amino phthalazine of the formula:—



- wherein the group  $R_4$  is a cyclic saturated organic base group linked to the phthalazine nucleus by the nitrogen atom, or a di-lower alkyl amino group; wherein  $R_1$  is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein  $R_2$  is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group of the  $R_1$  substituent when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group may be substituted with one or more lower alkyl groups, which process comprises reacting a compound of the formula:

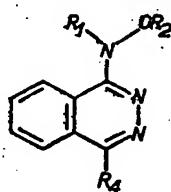


- 20 with a substituted hydroxylamine of the formula:—

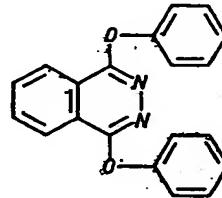


- in the presence of an inert non-reactive solvent and in the presence of anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

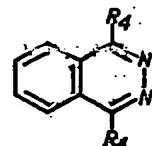
- 25 25. A process for producing a substituted 1-amino phthalazine of the formula:—



- 30 wherein the group  $R_4$  is a cyclic saturated organic base group linked to the phthalazine nucleus by the nitrogen atom, or a di-lower alkylamino group; wherein  $R_1$  is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein  $R_2$  is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group of the  $R_1$  substituent when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group may be substituted with one or more lower alkyl groups, which process comprises reacting a 1,4-diphenoxypyphthalazine of the formula:—



with a di-lower alkyl amine or a cyclic saturated organic base, at reflux temperatures so as to produce an intermediate compound of the formula:—

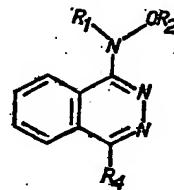


and then reacting said intermediate compound with a substituted hydroxylamine of the formula:—

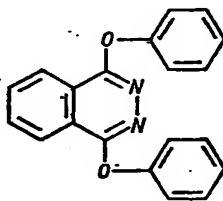


in the presence of an inert non-reactive solvent and in the presence of anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

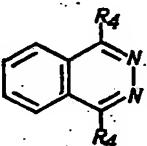
26. A process for producing a substituted 1-amino phthalazine of the formula:—



wherein the group  $R_4$  is a cyclic saturated organic base group linked to the phthalazine nucleus by the nitrogen atom, or a di-lower alkyl amino group; wherein  $R_1$  is hydrogen, a lower alkyl group, a phenyl group or a phenyl-lower alkyl group; wherein  $R_2$  is hydrogen, a lower alkyl group or an alkanoyl group; wherein the benzenoid portion of the phthalazine nucleus and/or the phenyl group of the  $R_1$  substituent when present may be unsubstituted or substituted with one or more halogen atoms or lower alkyl, lower alkoxy, nitro, amino, di-lower alkyl amino, or carboxy groups; and wherein the cyclic saturated organic base group may be substituted with one or more lower alkyl groups, which process comprises reacting a 1,4-dihalo phthalazine with sodium phenolate so as to produce a 1,4-diphenoxypyphthalazine of the formula:—



subsequently reacting said 1,4-diphenoxylphthalazine with a di-lower alkyl amine or a cyclic saturated organic base at reflux temperature so as to produce an intermediate compound of the formula:—



and finally reacting said intermediate compound with a substituted hydroxylamine of the formula:—



in the presence of an inert non-reactive solvent and in the presence of anhydrous sodium acetate, so as to produce the desired substituted 1-amino phthalazine.

27. A process for producing a substituted 1-amino phthalazine substantially as hereinbefore described with reference to any one of the Examples.

28. A substituted 1-amino phthalazine whenever prepared by a process as claimed in any one of claims 19 to 27.

29. A non-toxic pharmaceutically acceptable acid addition salt of a substituted 1-amino phthalazine as claimed in any one of claims 1 to 17 or as claimed in claim 28.

30. An acid addition salt as claimed in claim 29 which is the acid addition salt of an organic hydroxy or dibasic acid.

31. An acid addition salt as claimed in claim 30 which is the acid addition salt of citric, tartaric, malic or maleic acid.

32. A non-toxic pharmaceutically acceptable quaternary ammonium salt of a substituted 1-amino phthalazine as claimed in any one of claims 1 to 17 or as claimed in claim 28.

33. A quaternary ammonium salt as claimed in claim 32 which is a quaternary ammonium salt of methyl iodide or n-hexyl bromide.

34. A pharmaceutical composition in unit dosage form, for example as a tablet, suspension, solution or suppository, comprising a substituted 1-amino phthalazine as claimed in any one of claims 1 to 17 or as claimed in claim 28 together with a pharmaceutical diluent or carrier.

35. A pharmaceutical composition in unit dosage form, for example as a tablet, suspension, solution or suppository, comprising an acid addition salt of a substituted 1-amino phthalazine as claimed in any one of claims 29 to 31, together with a pharmaceutical acceptable diluent or carrier.

36. A pharmaceutical composition in unit dosage form, for example as a tablet, suspension, solution or suppository, comprising a quaternary ammonium salt of a substituted 1-amino phthalazine as claimed in claim 32 or claim 33.

37. A method of treating vertebrates other than man which comprises administering a compound as claimed in any one of claims 1 to 17 or as claimed in claim 28, or an acid addition salt as claimed in any one of claims 29 to 31, or a quaternary ammonium salt as claimed in claim 32 or claim 33.

38. A method of treating vertebrates other than man which comprises administering a pharmaceutical composition in unit dosage form, as claimed in any one of claims 34 to 36.

BOULT, WADE & TENNANT,  
111 & 112 Hatton Garden, London, E.C.1.,  
Chartered Patent Agents,  
Agents for the Applicant(s).

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